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| 10/519,641 | 07/15/2005 | Bruno Huet De Barochez | SERVIER 437 PCT | 9411 |

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| EXAMINER | |
|---|---|
| PALENIK, JEFFREY T | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1615 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/519,641 | HUET DE BAROCHEZ ET AL. | |
| | Examiner | Art Unit | |
| | Jeffrey T. Palenik | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *17-32 and 34-38* is/are pending in the application.

4a) Of the above claim(s) *27,29 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-26,28,30,32 and 34-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### STATUS OF THE APPLICATION

Receipt is acknowledged of Applicant's Request for Continued Examination (RCE) and Remarks, filed 19 February 2010 for Application N° 10/519,641. The Examiner further acknowledges the following:

No additional claims have been amended, added or canceled.

No new matter has been added.

Thus, claims 17-26, 28, 30, 32 and 34-37 continue to represent all claims currently under consideration.

### INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statement (IDS) have been submitted for consideration.

### MAINTAINED REJECTIONS

The following rejection is maintained from the previous Office Correspondence dated 17 August 2009 since the art which was previously cited continues to read on the amended limitations.

### CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-26, 28, 30, 32 and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garthwaite et al. (US Pre-Grant Publication 2002/0132001) in view of Guez et al. (USPN 6,653,336).

The instant claims are drawn to reservoir microcapsule composition comprising microparticles of the angiotensin control enzyme (ACE) inhibitor perindopril, wherein said microparticles are covered by a film coating comprising a hydrophilic polymer and a hydrophobic polymer, the second of which is present at less than or equal to 40% by weight

of the microcapsule, and have a diameter of less than 1200 microns (claims 17 and 23-25). With regard to the limitations recited in claim 23-25, which state that the "coating film enables" a pH-related dissolution profile comprising a latent phase duration of a half hour or longer, and a release phase of perindopril; until some material differences in the properties of the composition are demonstrated, said limitation is considered by the Examiner to be directed toward a composition of perindopril microcapsules coated with a combination of hydrophilic and hydrophobic polymers, which is instantly claimed. Furthermore, the limitation recited in claim 17, wherein the hydrophobic polymer is present at less than or equal to 40% by weight, is interpreted by the Examiner as including 0% by weight. The hydrophilic polymer is recited as being a copolymer such as methacrylic acid and methyl methacrylate (claims 18 and 19). The hydrophobic polymer is recited as being hydrogenated vegetable oil (claims 20 and 21). Claim 22 recites a ratio range for the hydrophilic and hydrophobic polymers in the coating. Claim 26 recites the elected tert-butylamine salt of perindopril. Claim 28 recites the perindopril active deposited on a neutral core ranging in diameter from 50-600 microns. Composition of the neutral core is recited in claim 30. Claim 32 recites the composition of claim 17 further comprising indapamide microcapsules. Independent claim 34 recites a pharmaceutical composition comprising the perindopril microcapsules of claim 17 and further comprising at least one pharmaceutically acceptable excipient. Dosage forms for the composition of claim 34 are recited (claims 35 and 36). Independent claim 37 recites a method of treating arterial hypertension comprising administering the composition of claim 17 to an animal such as a human.

Garthwaite et al. teach a composition comprising dual antihypertensive agents wherein the first of said agents is taught as eplerenone and the second of which is taught as preferably being a different antihypertensive agent such as a diuretic or an ACE inhibitor (claims 1, 9, 10 and 14). Perindopril is an example of an ACE inhibitor and indapamide is an example of a diuretic, both of which are taught in the Table in ¶[0087]. The same table also teaches eplerenone as an example of a diuretic compound. The composition is further taught as a capsule comprising enterically coated pellets (claim 17). Said pellets are taught as having a preferred core formulation comprising cellulose or cellulose derived material ¶[0132] and more preferably lactose or microcrystalline cellulose ¶[0133]. The uncoated cores are taught as being in the form of generally spherical beads having a diameter of 1,000 microns or less and preferably ranging from about 200-800 microns ¶[0141]. In the case of the coated, active-loaded core, typical diameters, particularly in the case of pellets or beads, ranges from 200 to 1700 microns ¶[0140]. Enteric coatings on the cores are taught as being used to control the release of the antihypertensive formulations contained therein ¶[0146]. The coating is taught as being produced from copolymers of acrylic acid and methacrylic acid or esters of either monomer, which are referred to overall as "polymerized acrylates" ¶[0147]. Specific examples of polymerized acrylates include Eudragit® L and Eudragit® S, the commercial brand names for methacrylic acid/methyl methacrylate copolymer (see *Degussa Specifications and Test Methods*). In addition to the polymers, the coating layer typically includes a lubricant such as hydrogenated vegetable oils ¶¶[0155], [0124] and [0125]. The polymeric coating is taught as comprising about 10-50% by weight of polymerized acrylates ¶[0148] and the lubricants, if present, are taught as ranging between 0.1-10% by weight

¶[0126]. Mixed together in the enteric coating, a ratio of polymerized acrylates to lubricant is established, such as 10%:10% or 1:1. Additional excipients are taught such as diluents, disintegrants, binding agents and wetting agents are taught ¶¶[0106] – [0123]. Dosage formulations such as tablets and hard gelatin capsules are taught by Examples 1-3 and 4-7, respectively. Claims 19-21 teach orally administering the composition discussed above as a means for treating humans for elevated blood pressure.

Garthwaite et al. do not expressly teach the microcapsules as comprising the elected tert-butylamine salt of perindopril or the claimed combination of said salt microcapsules with indapamide microcapsules.

Guez et al. teach orally administering a combination dosage comprising an ACE inhibitor and diuretic for the treatment of arteriolo-capillary microcirculatory disorders such as arterial hypertension (Abstract, col. 3, lines 1-10). The preferred combination of ACE inhibitor and diuretic is further taught as being Perindopril tert-butylamine salt and Indapamide, respectively (col. 3, lines 33-38). Examples 1 and 2, in particular, teach tablet formulations comprising Perindopril tert-butylamine salt and Indapamide in combination with hydrophobic polymeric lubricants such as magnesium stearate and hydrophilic polymeric cellulose compounds such as microcrystalline cellulose. Example 19 further teaches the preferred Perindopril salt-Indapamide combination as being significantly pertinent to decreasing arterial pressure (col. 7, lines 48-49). Though tablets are taught as the preferred form of oral administration, other routes such as capsules, including hard gelatin capsules are also taught (col. 3, lines 39-50).

Guez et al. do not expressly teach the two preferred active ingredients in the form of microencapsulated pellets or granules nor are the two actives expressly taught as being encapsulated separate from one another but within the same dosage form.

In view of the combined teachings of the prior art, it would have been obvious to one of ordinary skill in the art, at the time of the invention, to prepare a composition comprising hydrophilic/hydrophobic polymer encapsulated perindopril and indapamide microparticles, as taught and suggested by Garthwaite and Guez, modify the ratio of the coating ingredients, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Garthwaite teaches enterically coated particles comprising a first anti-hypertensive agent, specifically a diuretic, and an additional anti-hypertensive agent, such as an ACE inhibitor. The Table in ¶[0087], as discussed above, teaches the ACE inhibitor perindopril as well as the diuretic indapamide. The motivation for the skilled artisan to substitute a thiazide diuretic such as indapamide for a potassium-sparing diuretic such as eplerenone, is based on two points: (1) that despite their chemical distinction, both compounds target the renal system to accomplish the same fundamental end, namely increased excretion of water from the body, and (2) they share at least one chemical pathway by which said elevated water excretion is achieved, namely preventing the reabsorption of sodium and chloride ions (see *The Drug Monitor*). The skilled artisan would have been further motivated to combine indapamide specifically with the tert-butylamine salt of perindopril not only because Garthwaite and Guez teach overlapping technology, namely establishing tablet and/or gelatin capsule dosage forms

comprising both active agents admixed with hydrophilic and hydrophobic polymeric additives, but more importantly because Guez expressly teaches the combination of actives as being effective at alleviating arterial hypertension or pressure (see Example 19 of Guez). From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the combined references, especially in the absence of evidence to the contrary.

## RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claims 17-26, 28, 30, 32 and 34-37 under 35 USC 103(a) as being unpatentable over the combined teachings of Garthwaite et al. and Guez et al. have been fully considered but they are not persuasive.

Applicants continue to traverse the rejection on the basis that the Office has provided no motivation to combine the teachings of Garthwaite et al. and Guez et al. More specifically, Applicants argue that the reference is preferably drawn to an enterically coated formulation comprising an aldosterone antagonist active agent and an additional antihypertensive active agent. The aldosterone antagonist is further taught as being embodied by a diuretic (e.g. eplerenone) whereas the antihypertensive is taught as encompassing perindopril ¶[0087]. Applicants argue that the reference does not disclose a composition comprising any diuretic in combination with an ACE inhibitor, such as enterically coated particles which display delayed and controlled release characteristics. Concerning the delayed/extended release coatings

taught by the reference, Applicants argue that preference is given to immediate release coatings as it appears to be required where enteric coatings are applied to the core formulations. Concerning the "Drug Monitor" reference, Applicants assert that "different treatment options" and the reference's silence to a teaching that all diuretics are useful for the same purpose, is sufficient in overcoming the Examiner's argument that eplerenone and indapamide are functional equivalents.

Lastly, concerning the Guez reference, Applicants merely state that the Office acknowledges that the reference does not teach such compositions.

The Examiner respectfully disagrees with Applicants' arguments.

First, in response to Applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Second, the Garthwaite reference alone, teaches the microencapsulation of a diuretic and an antihypertensive within both delayed-release and extended-release core coatings, per ¶[0102]. Applicants' assertion that the delayed release coatings preferably comprise an immediate-release formulation is immaterial. The reference teaches particles demonstrating delayed drug release. Furthermore, Applicants' remarks directed to the use of extended-release cores is similarly unpersuasive, particularly in view of MPEP §2123. The Examiner agrees that extended-release cores are taught as being generally not preferred. However, ER cores are also taught as being a useful formulation in certain circumstances, which means that

the reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art (e.g., including nonpreferred embodiments).

Third, regarding the active agents used in the Garthwaite reference, the Examiner acknowledges that the instant claimed combination of tert-butyl salt of perindopril and indapamide is not expressly taught. However, in considering the guidance provided by the combination of the references (e.g. Garthwaite and Guez, as evidenced by *The Drug Monitor*), the instant invention is rendered *prima facie* obvious to the ordinarily skilled artisan.

Garthwaite teaches and suggests the microencapsulated combination of eplerenone and perindopril, as discussed previously. The Table of ¶[0087], as further evidenced by the teachings of *The Drug Monitor*, teaches that eplerenone and indapamide are functional equivalents of one another in that they are both diuretic type active ingredients. That is, absent a showing of evidence to the contrary, the ordinarily skilled artisan substituting indapamide for the preferred eplerenone in the formulation taught by Garthwaite would have a reasonably high expectation that a formulation conveying the effects of a diuretic compound would result. As Garthwaite does not expressly teach the instantly claimed combination of perindopril and indapamide, motivation to combine the suggested teachings of Garthwaite is further provided in the teachings of Guez.

Guez is directed to delayed release formulations, preferably oral formulations, which consist of indapamide and the *tert*-butyl salt of perindopril as the active ingredients. The formulations in both references are taught as being used to alleviate various circulatory conditions.

In view of the forgoing, the Examiner maintains that it would have been *prima facie* obvious for the ordinarily skilled artisan to arrive at the instantly claimed dual population of microparticles. The combined teachings of Garthwaite and Guez would highly motivate the ordinarily skilled artisan to create the individually coated microparticles since Garthwaite expressly suggests the structural teachings of the individually coated actives as well as the suggestion that eplerenone and indapamide are functionally equivalent diuretics. Both Garthwaite and Guez teach that the final oral dosage form may be in the form of a gelatin capsule. Thus, both references also minimally provide at least one teaching of "controlled release".

Applicants' Rule 132 Declaration submitted on 1 May 2009, has been fully reconsidered but is still not persuasive. Though presenting data with regards to a form of controlled release for perindopril, the study is not considered to be commensurate in scope with the instant claims for the following reasons:

- The study is directed to the release of perindopril and/or perindoprilat (e.g. the in vivo, enzymatically released form of perindopril). Otherwise stated, it at no time addresses the release of the instantly claimed indapamide active ingredient.
- Though the study clearly contrasts immediate- versus delayed-release preparations of perindopril/perindoprilat, the Examiner also acknowledges that type I and type II delayed-release microparticle formulations are contrasted. The study is not considered persuasive because there is no clear reconciliation between these two types of microparticles which seemingly have different release profiles. That is to

say, it is clear that the two formulations contain different amounts of active and that the two formulations demonstrate different release profiles. However, the differences between the Type I and Type II formulations, beyond the drug amount, have not been made clear. Otherwise stated, what about the formulations is causing a different release pattern?

- Lastly, Applicants' study asserts that "[a] latent period of about 4 hours is observed wherein the active principle, perindopril, **is not released in the plasma** and said latent period is followed by a controlled-release period of about 12 hours" [**emphasis added**]. A similar statement is made regarding the perindoprilat as well. After reviewing the submission, particularly the two release profile graphs, the Examiner respectfully submits that it appears in the case of both forms of perindopril that they are being released and a plasma concentration is able to be measured during the alleged "latent period". Regarding perindopril, for example, the type I microparticles plateau in their release of the active well before the four-hour time point. The type II microparticles as well, are also measurably releasing the drug prior to the four-hour time point which marks the end of the "latent period".

For these reasons, Applicants' arguments are found unpersuasive. Said rejection is therefore **maintained**.

All claims under consideration remain rejected; no claims are allowed.

## CONCLUSION

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

## CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner, Art Unit 1615